

PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

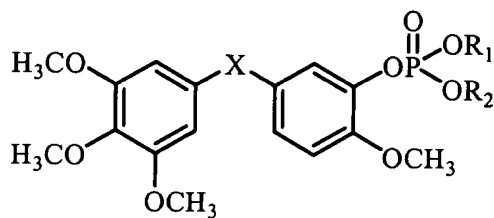
AMENDMENTS TO THE CLAIMS:

The following is a complete listing of the claims.

Claims 1-10 (Cancelled)

11. (New) A process for preparing a compound of Formula III,

(III)



wherein:

X represents a *cis*- or *trans*- alkenyl group represented by $-(CH=CH)_1-$;

one of $-OR_1$ or $-OR_2$ is O^-Q^+ or $-O-Q$, and the other is hydroxyl, $-O^-Q^+$, or $-O-Q$;
and

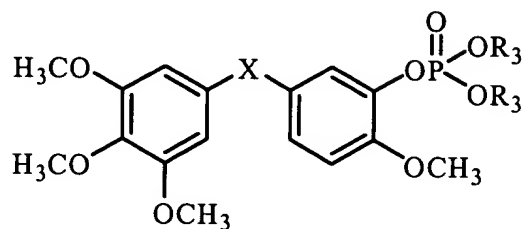
Q is an alkali metal, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic,

the process comprising:

a) contacting *cis*- or *trans*-combretastatin A-4 in a solvent with a di(arylmethyl)phosphite in the presence of a tetrahalomethane, a tertiary amine, and an acylation catalyst to form a protected phosphate ester of Formula I,

103

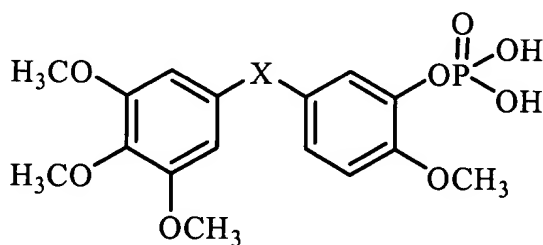
PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950



(I)

wherein R_3 is an arylmethyl phosphate protecting group; and

b) contacting the protected phosphate ester of Formula I with a trialkylhalo silane for a period of time sufficient to generate the phosphoric acid compound of Formula II.



(II)

12. (New) The process of claim 11 further comprising the step of contacting the phosphoric acid compound of Formula II with an alkali metal hydroxide, alkali metal alkoxide, alkali earth metal hydroxide, alkali earth metal alkoxide, transition metal hydroxide, transition metal alkoxide, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, a nitrogen-containing antibiotic, or a salt thereof to generate a compound of Formula III.

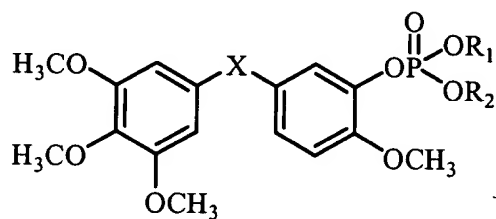
203

PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

13. (New) The process of claim 11, wherein the phosphoric acid compound of Formula II is contacted with sodium methoxide to generate a disodium phosphate salt or a monosodium phosphate salt of combretastatin A-4.
14. (New) The process of claim 11 wherein the di(arylmethyl)phosphite is dibenzyl phosphite.
15. (New) The process of claim 11 wherein the tetrahalomethane is selected from the group consisting of CCl₄, CBr₄, CF₄, and Cl₄.
16. (New) The process of claim 11 wherein the tertiary amine is selected from the group consisting of N,N-diisopropylethylamine, triethylamine, pyridine, N-methyl morpholine, and DBU.
17. (New) The process of claim 11 wherein the acylation catalyst is N,N-dimethylaminopyridine.
18. (New) The process of claim 11 wherein the trialkylhalo silane is selected from the group consisting of trimethylbromo silane, trimethylchloro silane, trimethyliodo silane, trimethylfluoro silane, and mixtures thereof.
19. (New) The process of claim 11 wherein the solvent is a halogenated or non-halogenated solvent.

PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

20. (New) The process of claim 19 wherein the solvent is acetonitrile.
21. (New) The process of claim 11, wherein Q is selected from the group consisting of calcium, cesium, lithium, sodium, magnesium, manganese, and zinc.
22. (New) A process for preparing a compound of Formula III,



(III)

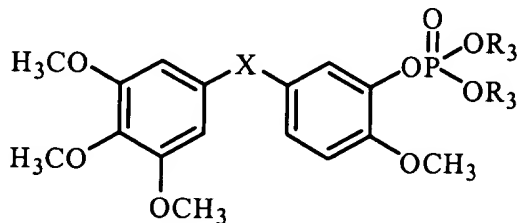
wherein:

X represents a *cis*- or *trans*- alkenyl group represented by -(CH=CH)₁-; and

R₁ and R₂ are hydrogen;

the process comprising:

a) contacting *cis*- or *trans*-combretastatin A-4 in a solvent with a di(arylmethyl)phosphite in the presence of a tetrahalomethane, a tertiary amine, and an acylation catalyst to form a protected phosphate ester of Formula I,

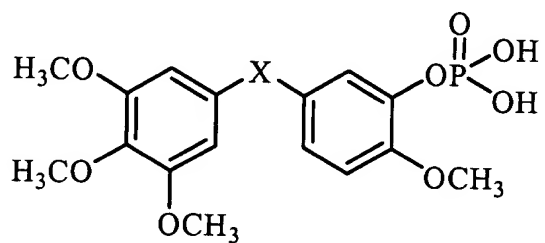


PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

(I)

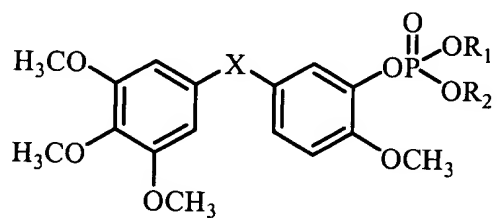
wherein R_3 is an arylmethyl phosphate protecting group; and

b) contacting the protected phosphate ester of Formula I with a trialkylhalo silane for a period of time sufficient to generate the phosphoric acid compound of Formula II.



(II)

23. (New) A process for preparing a compound of Formula III,



(III)

wherein:

X represents a *cis*- or *trans*- alkenyl group represented by $-(CH=CH)_1-$;

one of $-OR_1$ or $-OR_2$ is O^-Q^+ or $-O-Q$, and the other is hydroxyl, $-O^-Q^+$, or $-O-Q$ and

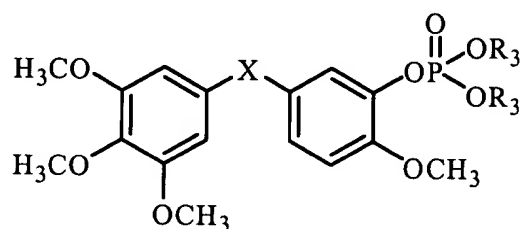
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PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

Q is an alkali metal, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic,

the process comprising:

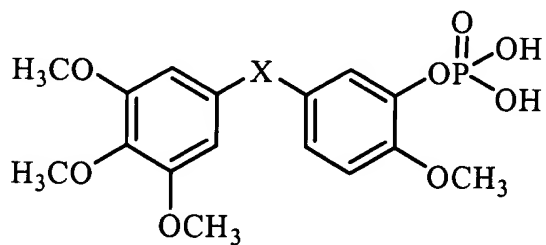
- (a) contacting *cis*- or *trans*-combretastatin A-4 in a solvent with 1*H*-tetrazole, a phosphine, and an oxidizing agent at a temperature for a period of time sufficient to form a protected phosphate ester of Formula I,



(I)

wherein R_3 is an aryl, arylmethyl or alkyl phosphate protecting group; and

- (b) contacting the protected phosphate ester of Formula I with an acidic compound or a trialkylhalo silane for a period of time sufficient to generate the phosphoric acid compound of Formula II,



(II)

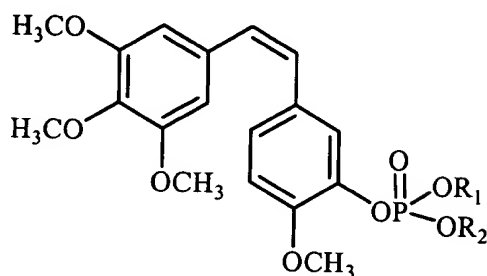
24. (New) The process of claim 23, further comprising the step of contacting the phosphoric acid compound of Formula II with an alkali metal hydroxide, alkali metal alkoxide, alkali

PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

earth metal hydroxide, alkali earth metal alkoxide, transition metal hydroxide, transition metal alkoxide, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, a nitrogen-containing antibiotic, or a salt thereof to generate a compound of Formula III.

25. (New) The process of claim 23, wherein the phosphine is selected from the group consisting of di-tert-butyloxy(N,N-diethylamido)phosphine, di-tert-butyloxy(N,N-diisopropylamido)phosphine, bis-[2-(trimethylsilyl)ethoxy]-N,N-diisopropylamidophosphine, and dibenzyl-N,N-diethylphosphoramidite.
26. (New) The process of claim 23, wherein the oxidizing agent is selected from the group consisting of mCPBA, hydrogen peroxide, t-butyl hydroperoxide, and peroxyacids.
27. (New) The process of claim 23 wherein the temperature is about -70 °C to about 25 °C.
28. (New) The process of claim 23 wherein the solvent is a halogenated solvent, a non-halogenated solvent, or a mixture thereof.
29. (New) The process of claim 28 wherein the solvent is a mixture of tetrahydrofuran and dichloromethane.
30. (New) A process for preparing a compound of Formula VI

PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950



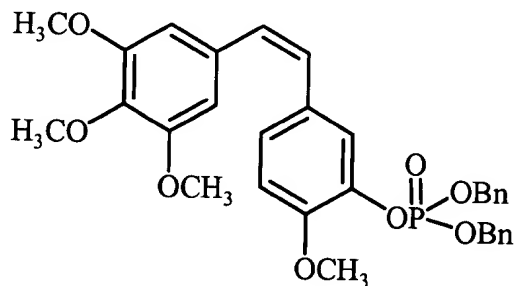
(VI)

wherein,

one of $-OR_1$ or $-OR_2$ is O^-Q^+ or $-O-Q$, and the other is hydroxyl, $-O^-Q^+$, or $-O-Q$ and Q is an alkali metal, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic,

the process comprising:

(a) contacting *cis*-combretastatin A-4 in a solvent with di(benzyl)phosphite in the presence of tetrahalomethane, a tertiary amine, and an acylation catalyst to form a protected phosphate ester of Formula IV;

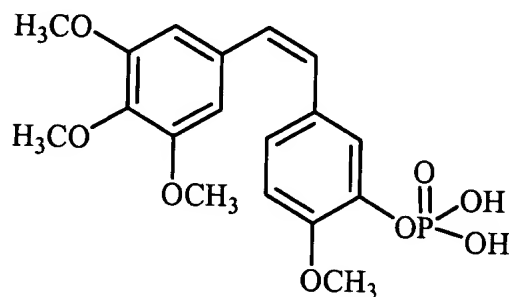


(IV)

(b) contacting the protected phosphate ester of Formula IV with a trialkylhalo silane for a period of time sufficient to generate the phosphoric acid compound of Formula V; and

03

PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

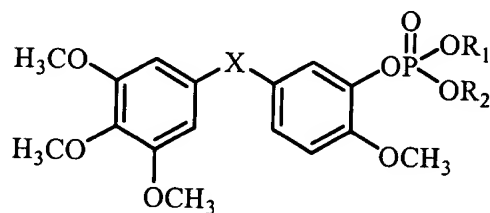


(V)

(c) contacting the phosphoric acid compound of Formula V with an alkali metal hydroxide, alkali metal alkoxide, alkali earth metal hydroxide, alkali earth metal alkoxide, transition metal hydroxide, transition metal alkoxide, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, a nitrogen-containing antibiotic, or a salt thereof to generate a compound of Formula VI.

31. (New) A compound of Formula III,

(III)



wherein:

X represents a *cis*- or *trans*- alkenyl group represented by $-(CH=CH)_1-$;

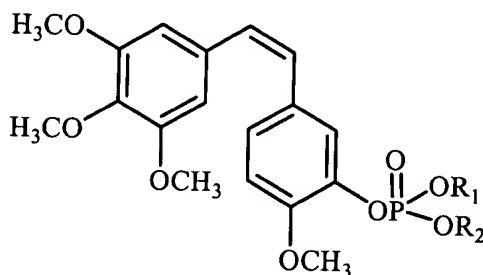
one of $-OR_1$ or $-OR_2$ is O^-Q^+ or $-O-Q$, and the other is hydroxyl, $-O^-Q^+$, or $-O-Q$;
and

Q is an alkali metal other than sodium or potassium, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an

PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

amino-sugar, an amino-nitrile, a nitrogen-containing antibiotic, or any combination thereof.

32. (New) The compound of claim 31, wherein Q is selected from the group consisting of cesium, lithium, magnesium, calcium, chromium, manganese, iron, cobalt, nickel, copper, zinc, platinum; silver, gold, imidazole, pyridine, pyrazole, morpholine, piperidine, piperazine, adenosine, tetracycline and verapamil, cinchonine, glucosamine, quinine and guanidine.
33. (New) A compound having a general structure of the formula VI:



(VI)

wherein:

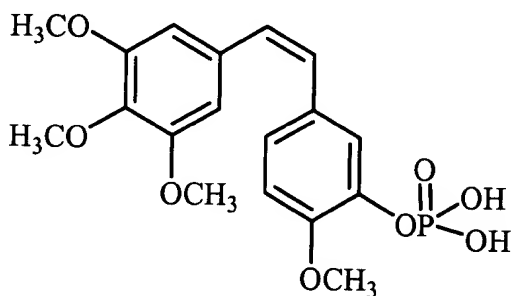
one of -OR₁ or -OR₂ is O⁻Q⁺ or -O-Q, and the other is hydroxyl, -O⁻Q⁺, or -O-Q; and

Q is an alkali metal, an alkali earth metal, a transition metal, a heteroaryl, a heterocycl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic.

34. (New) A pharmaceutical composition comprising the compound of claim 31 and a pharmaceutically acceptable carrier thereof.

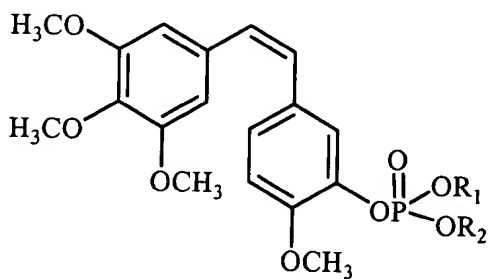
PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

35. (New) A pharmaceutical composition comprising the compound of claim 33 and a pharmaceutically acceptable carrier thereof.
36. (New) A process for preparing a compound of claim 33, comprising the step of contacting, in a solvent, combretastatin A-4 phosphate free acid having the structure:



with an alkali metal hydroxide, alkali metal alkoxide, alkali earth metal hydroxide, alkali earth metal alkoxide, transition metal hydroxide, or transition metal alkoxide which is capable of forming a metal salt with the phosphoric acid.

37. (New) A method of modulating tumor growth or metastasis in an animal comprising the administration of an effective amount of a compound having a general structure of the formula VI:



(VI)

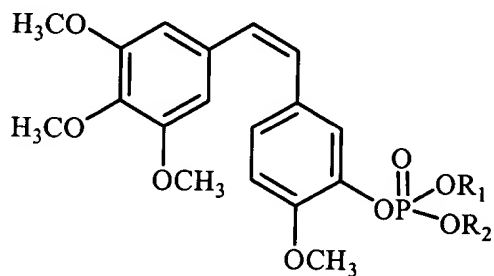
PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

wherein:

one of $-OR_1$ or $-OR_2$ is O^-Q^+ or $-O-Q$, and the other is hydroxyl, $-O^-Q^+$, or $O-Q$; and

Q is an alkali metal, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic.

38. (New) The method of claim 37, wherein Q is a metal selected from the group consisting of lithium, cesium, manganese, magnesium, calcium, and zinc.
39. (New) The method of claim 37, wherein Q is a heteroarylene or a heterocyclyl selected from the group consisting of imidazole, morpholine, piperazine, piperidine, pyrazole, and pyridine.
40. (New) A method of modulating microbial growth in an animal comprising the administration of an effective amount of a compound having a general structure of the formula VI:



(VI)

wherein:

PRELIMINARY AMENDMENT IN RESPONSE TO OFFICE ACTION
U.S. Non-Provisional Application Serial No. 09/582,950

one of $-OR_1$ or $-OR_2$ is O^-Q^+ or $-O-Q$, and the other is hydroxyl, $-O^-Q^+$, or $-O-Q$; and

Q is an alkali metal, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic.

93